Office Action Summary	Application No.	Applicant(s)
	10/562,951	ANDERTON ET AL.
	Examiner	Art Unit
	DAVID J. STEADMAN	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,26,27,31-36,38-46 and 53-55* is/are pending in the application.

4a) Of the above claim(s) *31,33-35,40,43-46,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,26,27,32,36,38,39,41,42 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 22, 26-27, 31-36, 38-46, and 53-55 are pending in the application.

[2] Applicant's amendment to the claims, filed on 4/18/11, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Applicant is advised to comply with the amendment requirements according to 37 CFR 1.121. It is noted that the term "contacting" has been deleted from claim 22, part (a) without showing strikethrough.

[3] Applicant's remarks filed on 4/18/11 have been fully considered and are deemed to be persuasive to overcome at least one rejection and/or objection previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[5] Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/10/08.

[6] Claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 are being examined on the merits.

Claim Objections

[7] The objection to claim 55 as not reciting a conjunction before the last species of phosphorylation sites is withdrawn in view of the instant claim amendment.

[8] Claim 27 is newly objected to in the recitation of "having one or more said phosphorylation sites" and in the interest of improving claim form, it is suggested that the noted phrase be amended to recite, "having one or more of said phosphorylation sites".

[9] Claim 39 is newly objected to in the recitation of "wherein the step of determining the presence, absence or extent of phosphorylation" and in the interest of maintaining consistency and improving claim form, it is suggested that the noted phrase be amended to recite, "wherein the step of determining whether, and optionally the extent of phosphorylation".

Claim Rejections - 35 USC § 112, Second Paragraph

[10] Claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by the instant claim amendment to delete the term "contacting" in step (a) of claim 22.

Claim 22 (claims 26-27, 32, 36, 38-39, 41-42, and 55 dependent therefrom) is confusing in view of applicant's amendment to omit the term "contacting" in step (a). It is suggested that, *e.g.,* claim 22 be amended to insert the term "contacting" immediately after "(a)".

Claim Rejections - 35 USC § 103

[11] The rejection of claims 22, 26, 32, 36, 38-39, and 55 under 35 U.S.C. 103(a) as being unpatentable over Anderton et al. (US Patent 5,994,084; cite B of Form PTO-892 mailed on 10/3/08; hereafter "Anderton") in view of Singh et al. (*Mol. Cell. Biochem.* 131:181-189, 1994; cite U of Form PTO-892 mailed on 11/22/10; hereafter "Singh1"), Singh et al. (*Mol. Cell. Biochem.* 154:143-151, 1996; cite C8 of the IDS filed on 4/20/06; hereafter "Singh2"), Graves (*J. Biol. Chem.* 268:6394-6401, 1993; cite W of Form PTO-892 mailed on 10/3/08hereafter "Graves"), Vitek et al. (US Patent 6,593,512; cite A of Form PTO-892 mailed on 10/3/08; hereafter "Vitek"), and Litersky et al. (*Biochem. J.* 316:655-660, 1996; cite V of Form PTO-892 mailed on 11/22/10; hereafter "Litersky") is maintained for the reasons of record and the reasons set forth below.

The reference of Anderton teaches a screening assay to identify therapeutic agents for Alzheimer's disease, the screening assay uses a cell recombinantly expressing tau protein and a kinase that modulates the phosphorylation of the tau protein (column 2, lines 39-61; column 7, lines 3-56). Anderton acknowledges the concept of using a combination of kinases in the screening method (see claim 4). Anderton teaches the screening assay can be an immunoassay (column 7, lines 22-24)

using antibodies, including monoclonal antibodies, that may be produced against phosphorylated and non-phosphorylated tau epitopes (column 7, lines 24-26). Anderton teaches screening may be carried out by incubating the cell with a potential therapeutic agent and then incubating the cells with tau-specific and hyperphosphorylated tau-specific antibodies and the extent of binding of the antibodies indicates the extent to which hyperphosphorylation has occurred (column 7, lines 39-46).

The reference of Anderton does not teach or suggest:

1) using a combination of Casein Kinase 1 (CK1) and calcium/calmodulin-dependent protein kinase II (CaM kinase II);

2) the CK1 of SEQ ID NO:1;

3) the tau of SEQ ID NO:2; and

4) detecting phosphorylation of tau at a residue recited in claim 22, *e.g.,* S416.

Regarding using a combination of CK1 and CaM kinase II in the method of Anderton, the references of Singh1 and Singh2 teach the significance of the specific combination of CK1 and CaM kinase II on tau phosphorylation. Specifically, Singh1 teaches that each of CK1 and CaM kinase II separately phosphorylate tau (p. 183, Table 1) and teaches a combination of CK1 and CaM kinase II phosphorylated tau to higher stoichiometries relative to the single kinase (p. 185, column 1; p. 185 Figures 3 and 4). According to Singh1, when tau is phosphorylated by CK1, the addition of CaM kinase II (and vice versa) resulted in additional, rapid phosphorylation of tau (p. 185, column 1 and Figure 3; sentence bridging columns 1-2 and Figure 4). Singh2 teaches that tau can be converted to an Alzheimer-like state after phosphorylation by CK1 (p.

149, column 2, bottom), the CK1 phosphorylation sites on tau are some of the same sites found in paired helical filament tau (PHF-tau) (p. 149, column 1, bottom), and the sites of CK1 phosphorylation in PHF-tau were phosphorylated more rapidly and to a greater extent if tau is pre-phosphorylated by CaM kinase II (p. 143, abstract).

Regarding detecting phosphorylation of tau at a residue recited in claim 22, *e.g.*, S416, the reference of Litersky teaches tau is phosphorylated at S416 by CaM kinase II (p. 659, column 2, top). Also, with respect to claim 36, Litersky teaches tau is also phosphorylated by CaM kinase II at S262 and S356.

Regarding CK1 of SEQ ID NO:1, the reference of Graves teaches cloning of a nucleic acid encoding a CK1 polypeptide (p. 6395-6396) that has a nucleotide sequence (p. 6397) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix A sequence alignment of the Office action mailed on 10/3/08).

Regarding tau of SEQ ID NO:2, Vitek teaches cloning of a nucleic acid encoding a tau polypeptide (Example 7, beginning at column 12) that has a nucleotide sequence (SEQ ID NO:7) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix B sequence alignment of the Office action mailed on 10/3/08).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky to practice the method of Anderton using a combination of CK1 and CaM kinase II and detecting CaM kinase II phosphorylation of at least S262, S356, and S416 of tau. Although the prior art does not appear to expressly teach S416 phosphorylation of tau by CK1, by determining whether a candidate substance inhibits CaM kinase II

phosphorylation of S262, S356, and S416 of tau in the presence of a *combination* of CaM kinase II and CK1, one would have practiced determining whether and optionally the extent to which a candidate substance inhibits phosphorylation of tau at S416. One would have been motivated to use a *combination* of CK1 and CaM kinase II in the method of Anderton because Singh1 and Singh2 teach the significance of the combination of CK1 and CaM kinase II on tau phosphorylation, *e.g.,* pre-phosphorylation of tau by CK1 enhances CaM kinase II phosphorylation of tau (or vice-versa), achieving greater phosphorylation of Tau than either kinase alone. One would have been motivated to detect CaM kinase II phosphorylation of S262, S356, and S416 of tau because these residues are specifically phosphorylated by CaM kinase II as acknowledged by Litersky. One would have had a reasonable expectation of success to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky to practice the method of Anderton using a combination of CK1 and CaM kinase II and detecting phosphorylation of at least S262, S356, and S416 of tau because of the results of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky. Therefore, the method of claims 22, 26, 32, 36, 38-39, and 55 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: At p. 8 of the instant remarks, applicant characterizes claim 22 as specifically identifying a select number of phosphorylation sites present on tau and requiring that a single enzyme, CK1 or a variant thereof, phosphorylate tau at one or more of the recited sites.

While the examiner agrees with applicant's characterization of claim 22 as reciting certain phosphorylation sites on tau protein, the examiner disagrees with applicant's characterization of claim 22 as requiring that a *single* enzyme phosphorylate tau at one or more of the recited sites. Contrary to applicant's position, while the claims require contacting a candidate substance, a tau protein or variant, and a CK1 polypeptide or variant, the claims do not exclude contacting with an additional kinase polypeptide, *e.g.,* CaM kinase II, particularly in light of the specification, which discloses, "...the present application also discloses that a combination of kinases is required to phosphorylate the majority of the phosphorylation sites disclosed herein...(paragraph bridging pp. 14-15).

Beginning at p. 8 of the instant remarks, applicant addresses the reference of Anderton, arguing Anderton is concerned only with mitogen activated kinase and brain proline-directed kinase phosphorylation of tau, not CK1. Applicant further argues the antibodies disclosed in Anderton will not "unambiguously identify all phosphorylated sites on tau listed in claim 22".

Applicant's argument is not found persuasive. Nowhere does Anderton teach or suggest that the method is only applicable to mitogen activated kinases and brain proline-directed kinases. To the contrary, Anderton teaches the method is generally applicable to any kinase that phosphorylates tau, expressly disclosing, "...an introduced DNA sequence encoding and capable of expressing a kinase that is capable...of modulating the phosphorylation of the protein tau..." (column 2, lines 48-50) and "The protocol may be carried out…using any other kinase capable or thought to be capable

of phosporylating tau..." (column 17, lines 25-28). In view of the teachings of Anderton, one of ordinary skill in the art would have recognized that the method of Anderton is applicable to any kinase that is capable of or is thought to be capable of phosphorylating tau.

Moreover, that Anderton (priority date of 1993) does not expressly include CK1 as a tau kinase is not surprising since up until Singh1 (1994), it was not known that CK1 phosphorylates Tau (p. 183, paragraph bridging columns 1-2).

Regarding applicant's argument that the antibodies disclosed in Anderton will not "unambiguously identify all phosphorylated sites on tau listed in claim 22", the claims do not require unambiguously identifying all phosphorylated sites on tau listed in claim 22. Rather, claim 22 recites "determining whether, and optionally the extent to which the candidate substance of i) inhibits phosphorylation....at *one or more* sites" (emphasis added).

Beginning at p. 9 of the instant remarks, applicant argues Singh1 and Singh2 do not teach any specific sites that are phosphorylated by CK1 either alone or in combination and that the antibodies disclosed in the Singh references will not identify all of the phosphorylated sites on tau listed in claim 22.

Applicant's argument is not found persuasive. The references of Singh1 and Singh2 are not relied on for disclosing specific CK1 phosphorylation sites on tau. Instead, Singh1 and Singh2 are cited as teaching the significance of the combination of CK1 and CaM kinase II on tau phosphorylation, *e.g.,* pre-phosphorylation of tau by CK1 enhances CaM kinase II phosphorylation of tau (or vice-versa), achieving greater

phosphorylation of Tau than either kinase alone. As noted above, Anderton acknowledges the concept of using a combination of tau kinases and in view of the teachings of Singh1 and Singh2, one would have been motivated to use the combination of CK1 *and* CaM kinase II in the method of Anderton to detect the extent of phosphorylation of S416, S262 and S356, which are known to be phosphorylated by CaM kinase II.

Regarding applicant's argument that the antibodies disclosed in the Singh references will not "unambiguously identify all phosphorylated sites on tau listed in claim 22", the claims do not require unambiguously identifying all phosphorylated sites on tau listed in claim 22. Rather, claim 22 recites "determining whether, and optionally the extent to which the candidate substance of i) inhibits phosphorylation....at *one or more* sites" (emphasis added).

At p. 10 of the instant remarks, applicant argues the claimed method is testing for substances that interfere with CK1 kinase phosphorylation of tau at specific sites.

Applicant's argument is not found persuasive. As noted in the prior Office action, although the prior art does not appear to expressly teach S416 phosphorylation of tau by CK1, by determining whether a candidate substance inhibits CaM kinase II phosphorylation of S416 of tau in the presence of a *combination* of CaM kinase II and CK1, one would have practiced the claimed method. "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose..." (MPEP 2144.IV).

At p. 10 of the instant remarks, applicant argues the skilled person would not be motivated to use another kinase in the assay because this would allegedly skew the interpretation of the data.

Applicant's argument is not found persuasive. To the contrary, Anderton expressly teaches the concept of using a combination of tau kinases in the claimed method (claim 4) and while Anderton does not expressly the teach the use of the combination of CK1 and CaM kinase II, Singh1 and Singh2 teach the significance of this combination on tau phosphorylation.

At p. 10 of the instant remarks, applicant argues Singh is not at all certain that CK1 is phosphorylating the sites in question, apparently referencing p. 149 of Singh2.

Applicant's argument is not found persuasive. As noted above, the references of Singh1 and Singh2 are not relied on for disclosing specific CK1 phosphorylation sites on tau. Instead, Singh1 and Singh2 are cited as teaching that the significance of the combination of CK1 and CaM kinase II on tau phosphorylation, *e.g.,* pre-phosphorylation of tau by CK1 enhances CaM kinase II phosphorylation of tau (or vice-versa), achieving greater phosphorylation of Tau than either kinase alone.

Beginning at p. 10 of the instant remarks, applicant argues there is no apparent reason to combine Graves and Vitek with Anderton, Singh1, and Singh2.

Applicant's argument is not found persuasive. The method of Anderton uses a nucleic acid encoding a kinase that phosphorylates tau and a nucleic acid encoding tau, yet does not disclose any nucleic acids encoding full-length tau and CK1.. The

references of Graves and Vitek are cited to show that nucleic acids encoding CK1 and tau were well-known at the time of the invention.

At p. 11 of the instant remarks, applicant argues the claimed method does not read on a combination of kinases.

Applicant's argument is not found persuasive. There is no claim limitation that excludes a *combination* of kinases in the claims. Moreover, claim 33, which depends from claim 22 and is currently withdrawn, indicates that applicant's claimed method is intended to encompass a combination of kinases.

At p. 11 of the instant remarks, applicant argues the claims require that CK1 be able to phosphorylate tau at the recited sites.

Applicant's argument is not found persuasive. The CK1 of Graves has the functional characteristic of phosphorylating tau at one or more of the recited sites. There is no evidence or line of reasoning to the contrary.

At p. 11 of the instant remarks, applicant addresses the reference of Litersky, arguing that Litersky does not mention CK1.

Applicant's argument is not found persuasive. Litersky is cited to show that, at the time of the invention, it was well known that CaM kinase II phosphorylates Tau at positions S262, S356, and S416.

At p. 11 of the instant remarks, applicant argues Litersky's observation that CaM kinase II phosphorylates tau provides no motivation for the skilled artisan to use CK1 in the screening assay of Anderton.

Applicant's argument is not found persuasive. At least for the reasons set forth above, it is the examiner's position that the reference of Litersky in combination with Anderton, Singh1, Singh2, Graves, and Vitek provides sufficient motivation to practice the claimed invention.

At p. 11 of the instant remarks, applicant argues the combination of references does not teach all claim limitations, referring to a comment by Litersky regarding phosphorylation at Ser-262 and Ser-356.

Applicant's argument is not found persuasive. Litersky expressly teaches that "we have demonstrated that...CamKII phosphorylate[s] Ser-262 and Ser-356 in tau" (p. 660, column 1) and "In this study, the ability of...CaMKII...to phosphorylate tau at Ser-262, as well as Ser-356, is demonstrated..." (p. 655, abstract).

Beginning at p. 11 of the instant remarks, applicant summarizes the grounds for traversing the obviousness rejection, which are fully addressed above.

At least for the reasons of record and the reasons set forth above, the examiner maintains the position that the combination of cited prior art teaches all claim limitations and provides a reasonable motivation and expectation of success and thus the claimed method would have been obvious to one of ordinary skill in the art at the time of the invention.

[12] The rejection of claims 22, 26-27, 32, 36, 38-39, and 55 under 35 U.S.C. 103(a) as being unpatentable over Anderton (*supra*) in view of Lau et al. (*Current Topics Med. Chem.* 2:395-415, 2002; cite V of Form PTO-892 mailed on 10/3/08; hereafter "Lau"),

Graves (*supra*), Vitek (*supra*), Hasegawa (*J. Biol. Chem.* 267:17047-17054, 1992; cite V of Form PTO-892 mailed on 5/12/09; hereafter "Hasegawa") and Yamamoto et al. (*Arch. Biochem. Biophys.* 408:255-262, 2002; cite W of Form PTO-892 mailed on 11/22/10; hereafter "Yamamoto") is maintained for the reasons of record and the reasons set forth below.

The relevant teachings of Anderton are set forth above.

The reference of Anderton does not teach or suggest:

1) CK1 as a tau-phosphorylating kinase;

2) the CK1 of SEQ ID NO:1;

3) the tau of SEQ ID NO:2; and

4) determining the phosphorylation state of a full-length purified tau by mass spectrometry.

Regarding CK1 as a tau-phosphorylating kinase, the reference of Lau teaches CK1 can phosphorylate tau, is tightly associated with paired helical filaments purified from Alzheimer's disease brains, three CK1 isoforms are upregulated in Alzheimer's disease brain, and that CK1 may be linked to tau pathology in Alzheimer's disease (p. 401, column 2, top). Lau further teaches "Since tau hyperphosphorylation is believed to be a critical step in neurofibrillary degeneration in AD, tau protein kinases become obvious therapeutic targets" (p. 403, column 2, bottom) and that since tau phosphorylation appears to be the primary contributor of paired helical filament/neurofibrillary tangle formation and microtuble disruption, inhibition of tau

phosphorylation has been proposed as a therapeutic target" (p. 405, paragraph bridging columns 1-2).

Regarding CK1 of SEQ ID NO:1, the relevant teachings of Graves are set forth above.

Regarding tau of SEQ ID NO:2, the relevant teachings of Vitek are set forth above.

Regarding determining the phosphorylation state of a full-length purified tau by mass spectrometry, at the time of the invention, one of ordinary skill in the art would have recognized the use of mass spectrometry as an alternative to immunoassay for analyzing the phosphorylation state of a polypeptide. See, *e.g.,* the references of Hasegawa and Yamamoto, which disclose using mass spectrometry to identify phosphorylated residues of a purified full-length tau polypeptide, which full-length tau protein includes S289 (see Hasegawa at p. 17051, Figure 5 and Yamamoto at p. 257). Regarding claim 27, the methods of Hasegawa and Yamamoto involve proteolytically cleaving tau into fragments (see, *e.g.,* Hasegawa at p. 17048, column 1 and Yamamoto at p. 256, column 2). Regarding claim 36, the term "substrate" has been interpreted as encompassing a phosphorylatable residue of tau and claim 36 encompasses determining the phosphorylation state of more than one of the phosphorylation sites recited in claim 22.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto to practice the method of Anderton using CK1 and compare the CK1-

phosphorylated tau in the presence and absence of a candidate inhibitor using mass spectroscopy according to Hasegawa and Yamamoto to determine the extent of tau phosphorylation. Although the prior art does not appear to expressly teach phosphorylation of S289 of tau by CK1, by comparing the CK1 phosphorylation of a full-length tau, which comprises all of the recited tau phosphorylation sites, in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau, including residue S289. One would have been motivated to use CK1 as a tau kinase in the method of Anderton because of the teachings of Lau as set forth above. One would have been motivated to compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because, as shown by Hasegawa and Yamamoto, this method is comprehensive, *i.e.,* determines phosphorylation state of residues of the full length of tau, and does not require an antibody for each particular phosphorylation site of tau. One would have had a reasonable expectation of success to Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto to practice the method of Anderton using CK1 and compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because of the results of Anderton, Lau, Graves, Vitek, Hasegawa, and Yamamoto. Therefore, the method of claims 22, 26-27, 32, 36, 38-39, and 55 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: At p. 12 of the instant remarks, applicant addresses the reference of Anderton, arguing Anderton is concerned only with mitogen activated kinases, not any and all possible kinases that may or may not phosphorylate tau.

Applicant's argument is not found persuasive. Nowhere does Anderton teach or suggest that the method is only applicable to mitogen activated kinases. To the contrary, Anderton teaches the method is generally applicable to any kinase that phosphorylates tau, expressly disclosing, "...an introduced DNA sequence encoding and capable of expressing a kinase that is capable...of modulating the phosphorylation of the protein tau..." (column 2, lines 48-50) and "The protocol may be carried out...using any other kinase capable or thought to be capable of phosporylating tau..." (column 17, lines 25-28). In view of the teachings of Anderton, one of ordinary skill in the art would have recognized that the method of Anderton is applicable to any kinase that is capable of or is thought to be capable of phosphorylating tau.

Moreover, that Anderton (priority date of 1993) does not expressly include CK1 as a tau kinase is not surprising since up until Singh1 (1994), it was not known that CK1 phosphorylates Tau (p. 183, paragraph bridging columns 1-2).

At p. 12 of the instant remarks, applicant argues the reference of Lau does not express certainty that CK1 is a valid therapeutic target.

Applicant's argument is not found persuasive. The examiner maintains the position that the teachings of Lau, when taken as a whole, suggest CK1 as a therapeutic target. Even assuming *arguendo* Lau does not suggest CK1 as a therapeutic target, Lau acknowledges that CK1 is a kinase that phosphorylates tau and

one of ordinary skill in the art would recognize that it would be applicable to the method of Anderton.

At p. 12 of the instant remarks, applicant argues there is no apparent reason to combine Graves and Vitek with the remaining references.

Applicant's argument is not found persuasive. The method of Anderton uses a nucleic acid encoding a kinase that phosphorylates tau and a nucleic acid encoding tau, yet does not disclose any nucleic acids encoding full-length tau and CK1. The references of Graves and Vitek are cited to show that nucleic acids encoding CK1 and tau were well-known at the time of the invention.

Beginning at p. 12 of the instant remarks, applicant addresses the reference of Yamamoto, arguing the reference is concerned with CaM kinase II, not CK1 and that Yamamoto's statement that CaM kinase II may be the most likely candidate for involvement in hyperphosphorylation of PHF-tau among protein kinases would not motivate one to consider CK1 as phosphorylating tau at residues 262 and 356. Applicant further argues Yamamoto does not disclose all 32 tau phosphorylation sites recited in claim 22.

Applicant's argument is not found persuasive. Yamamoto is cited to show that mass spectroscopic analysis of tau phosphorylation was fully enabled at the time of the invention and could resolve phosphorylation status of S262 and S356, not that one would seek to analyze the phosphorylation status of S262 and S356 after contact with CK1. By comparing CK1 phosphorylation of full-length tau, which comprises all of the recited tau phosphorylation sites, in the presence and absence of a candidate inhibitor

using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau at S289 in addition to S262 and S356.

Regarding applicant's argument that Yamamoto does not disclose all tau phosphorylation sites in claim 21, it is noted that the claims do not require identifying all phosphorylated sites on tau listed in claim 22. Rather, claim 22 recites "determining whether, and optionally the extent to which the candidate substance of i) inhibits phosphorylation....at *one or more* sites" (emphasis added) and by comparing CK1 phosphorylated full-length tau in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau at at least one of the sites recited in claim 22, *e.g.,* S289.

At p. 13 of the instant remarks, applicant addresses the reference of Hasgawa, arguing the phosphorylation sites on tau were not recognized until applicant's invention.

Applicant's argument is not found persuasive. The examiner maintains that by comparing CK1 phosphorylated full-length tau, which comprises all of the recited tau phosphorylation sites, in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining *whether or not* a candidate substance inhibits CK1 phosphorylation of tau at at least one of the sites recited in claim 22, *e.g.,* S289.

At least for the reasons of record and the reasons set forth above, the examiner maintains the position that the combination of cited prior art teaches all claim limitations

and provides a reasonable motivation and expectation of success and thus the claimed method would have been obvious to one of ordinary skill in the art at the time of the invention.

[13] The rejection of claim(s) 27 under 35 U.S.C. 103(a) as being unpatentable over Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims 22, 26, 32, 36, 38-39, and 55 above and further in view of Hasegawa is maintained for the reasons of record and the reasons set forth below.

The relevant teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims as applied to claims 22, 26, 32, 36, 38-39, and 55 are set forth above.

The combination of references does not appear to teach or suggest using a *fragment* of tau.

However, Hasegawa teaches that normal tau and PHF-tau isolated from human brain is post-translationally modified to begin with an alanine, not a methionine (p. 17054, column 1; p. 17053, Table I, A19).

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Hasegawa to use tau of SEQ ID NO:2 with a deletion of the N-terminal methionine. One would have been motivated to do this because of the teachings of Hasegawa that tau and PHF-tau are modified in the brain to remove an N-terminal methionine. One would have had a reasonable expectation of success to use express tau of SEQ ID

NO:2 with the N-terminal methionine removed because of the results of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Hasegawa. Therefore, the method of claim 27 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: Beginning at p. 13 of the instant remarks, applicant addresses the reference of Hasegawa, arguing tau with a deletion of the N-terminal amino acid is not a "fragment" as encompassed by claim 27. Applicant argues that even if the polypeptide of Hasegawa is a tau fragment, the reference does not enable identification of the relevant CK1 phosphorylation sites of tau.

Applicant's argument is not found persuasive. The specification fails to set forth a definition of the term "fragment" and the claim fails to recite a limitation that would exclude tau with a deletion of the N-terminal amino acid from being a "fragment" as encompassed by claim 27. Absent such a definition or claim limitation, the examiner maintains the position that tau with a deletion of the N-terminal amino acid is not a "fragment" as encompassed by claim 27.

At least for the reasons of record and the reasons set forth above, the examiner maintains the position that the combination of cited prior art teaches all claim limitations and provides a reasonable motivation and expectation of success and thus the claimed method would have been obvious to one of ordinary skill in the art at the time of the invention.

[14] The rejection of claims 41-42 under 35 U.S.C. 103(a) as being unpatentable over Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims 22, 26, 32, 36, 38-39, and 55 above OR Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 above and further in view of Zhu et al. (*Curr. Opin. Chem. Biol.* 5:4-45, 2001; cite X of Form PTO-892 mailed on 10/3/08; hereafter "Zhu") is maintained for the reasons of record and the reasons set forth below.

The teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims as applied to claims 22, 26, 32, 36, 38-39, and 55 are set forth above.

The teachings of Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 are set forth above.

Anderton further teaches the screening assay can be carried out on a large scale using microtitre plates and automated apparatus (column 7, lines 54-56). Anderton does not expressly teach immobilizing a plurality of substrates.

Zhu teaches "In the past, studies of protein activities have focused on studying a single protein at a time, which is often time-consuming and expensive" (p. 40, abstract). Zhu teaches the use of protein chips for protein kinase assay by, *e.g.,* attaching a substrate to a microwell plate and assaying kinase activity (p. 42, paragraph bridging columns 1-2 and p. 43, Figure 2). According to Zhu, "Coupled with mass-spectrometric identification, protein chips might also have wide application in drug discovery…Proteins and small-molecule ligands can be bound to proteins immobilized on a protein chip and the bound molecules identified using…mass spectroscopy" (p. 43, column 1, bottom).

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR the teachings of OR Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu to use a protein chip in an inhibitor screening method with tau protein as substrate. One would have been motivated to do this because of the teachings of Anderton and Zhu as set forth above. One would have had a reasonable expectation of success to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR the teachings of Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu to use a protein chip and mass spectroscopy in an inhibitor screening method with tau protein as substrate because of the results of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu. Therefore, the method of claims 41-42 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: At p. 14 of the instant remarks, applicant addresses the reference of Zhu, arguing Zhu does not teach using mass spectroscopy to measure CK1 phosphorylation of tau.

Applicant's argument is not found persuasive. While it is acknowledged that Zhu does not teach using mass spectroscopy to measure CK1 phosphorylation of tau, the rejection is based on a *combination* of references including Zhu. At least for the reasons of record and the reasons set forth above, the examiner maintains the position that the *combination* of cited prior art teaches all claim limitations and provides a reasonable

motivation and expectation of success and thus the claimed method would have been obvious to one of ordinary skill in the art at the time of the invention.

Claim Rejections – Double Patenting

[15] The obviousness-type double patenting rejection of claims 22, 26-27, 32, 36, 38-39, and 55 as being unpatentable over claim 6 of US Patent 5,994,084 (hereafter "'084 patent"; same as the reference of Anderton) in view of the teachings of Singh et al. (*FEBS Lett.* 358:267-272, 1995; cited in the IDS filed on 6/1/06; hereafter "Singh3"), Graves, Vitek, Hasegawa and Yamamoto is maintained for the reasons of record and the reasons set forth below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 6 of the '084 patent is drawn to a method of testing a potential therapeutic agent using target cells in vitro, comprising; 1) providing a cell as claimed in claim 1, said cell exhibiting hyperphosphorylation of the protein tau, 2) incubating said potential therapeutic agent with said cell, and 3) subsequently measuring the extent to which said

protein tau is phosphorylated, wherein a reduction in phosphorylation relative to that observed in a cell of claim 1 not incubated with said potential therapeutic agent indicates that said agent is a potential therapeutic. The cell of claim 1 of the '084 patent is a cell recombinantly expressing a tau and GSK-3α or GSK-3β.

The differences between claim 6 of the '084 patent and the claims of this application are:

1) the '084 patent does recite using a combination of GSK-3β and CK1 as a tau-phosphorylating kinase;

2) does not recite CK1 of SEQ ID NO:1;

3) does not recite tau of SEQ ID NO:2; and

4) does not recite determining the phosphorylation state of a full-length purified tau, which includes S289, by mass spectrometry.

Regarding using a combination of GSK-3α or GSK-3β and CK1 as a tau-phosphorylating kinase, the reference of Singh3 teaches that pre-phosphorylation of tau by CK1 stimulated phosphorylation of tau by GSK-3 as compared to tau that was not pre-phosphorylated and allows GSK-3 to rapidly phosphorylated some of the same epitopes seen in PHF-tau (p. 271, column 1, bottom).

Regarding CK1 of SEQ ID NO:1, the teachings of Graves are set forth above.

Regarding tau of SEQ ID NO:2, the teachings of Vitek are set forth above.

Regarding determining the phosphorylation state of a full-length purified tau by mass spectrometry, the teachings of Hasegawa and Yamamoto are set forth above.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify claim 6 of the '084 patent to use a combination of GSK-3α or GSK-3β and CK1; to use the CK1 of Graves and the tau of Vitek; and to determine the phosphorylation state of tau by mass spectrometry according to the method of Hasegawa and Yamamoto. One would have been motivated to use a combination of GSK-3α or GSK-3β and CK1 as a tau kinase in the method of claim 6 because of the teachings of Singh3 as set forth above. One would have been motivated to use the CK1 of Graves and the tau of Vitek because these are disclosed in the prior art as being CK1 and tau encoding sequences. One would have been motivated to compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because, as shown by Hasegawa and Yamamoto, this method is comprehensive, *i.e.,* determines phosphorylation of residues of the full length of tau, and does not require an antibody for each particular phosphorylation site of tau. One would have had a reasonable expectation of success to modify claim 6 of the '084 patent to use a combination of GSK-3α or GSK-3β and CK1; to use the CK1 of Graves and the tau of Vitek; and to determine the phosphorylation state of tau by mass spectrometry according to the method of Hasegawa and Yamamoto because of the results of Singh3, Graves, Vitek, Hasegawa, and Yamamoto.

RESPONSE TO REMARKS: At p. 15 of the instant remarks, applicant argues the claimed method does not analyze any and all sites of phosphorylation of tau, but is

drawn to identifying inhibitors that interfere with CK1 phosphorylation of tau at 32 distinct sites, several of which were unknown to be associated with Alzheimer's disease.

Applicant's argument is not found persuasive. The examiner maintains that by comparing CK1 phosphorylated full-length tau in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau at at least one of the sites recited in claim 22, *e.g.,* S289.

At p. 15 of the instant remarks, applicant further argues the claimed method is based on determining tau phosphorylation of a single kinase, CK1.

Applicant's argument is not found persuasive. As noted above, there is no claim limitation that excludes a *combination* of kinases in the claims. Moreover, claim 33, which depends from claim 22 and is currently withdrawn, indicates that applicant's claimed method is intended to encompass a combination of kinases. See also the specification's disclosure that "...the present application also discloses that a combination of kinases is required to phosphorylate the majority of the phosphorylation sites disclosed herein..." (paragraph bridging pp. 14-15).

At p. 15 of the instant remarks, applicant addresses the reference of Singh3, noting in particular the disclosure by Singh3 that "…How many of these seven kinases actually do participate in the hyperphosphorylation of PHF-tau is still unknown...Identification of the sites phosphorylated in tau by CK1 should clarify the issue".

Applicant's argument is not found persuasive. Singh3 supports CK1 phosphorylation of tau and, as noted above, Anderton discloses that the method is generally applicable to any kinase that phosphorylates tau, expressly disclosing, "...an introduced DNA sequence encoding and capable of expressing a kinase that is capable...of modulating the phosphorylation of the protein tau..." (column 2, lines 48-50) and "The protocol may be carried out...using any other kinase capable or thought to be capable of phosporylating tau..." (column 17, lines 25-28) and by comparing CK1 phosphorylation of full-length tau in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau at at least one of the sites recited in claim 22, *e.g.,* S289.

[16] The rejection of claims 41-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 of US Patent 5,994,084 in view of the teachings of Singh3, Graves, Vitek, Hasegawa, and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 and further in view of Zhu is maintained for the reasons of record and the reasons set forth below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The teachings of Singh3, Graves, Vitek, Hasegawa, and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 are set forth above.

The teachings of Zhu as applied to claims 41-42 are set forth above.

At the time of the invention, it would have been obvious to use a protein chip as taught by Zhu in the method of claim 6 of the '084 patent. One would have been motivated to do this in view of the advantages as taught by Zhu. One would have had a reasonable expectation of success to use a protein chip as taught by Zhu in the method of claim 6 of the '084 patent because of the results of Singh3, Graves, Vitek, Hasegawa, Yamamoto, and Zhu.

RESPONSE TO REMARKS: At p. 16 of the instant remarks, applicant argues "The inadequacy of this combination of references has been discussed above, particularly in sections A1 and D1 above.

Applicant's argument is not found persuasive. At least for the reasons of record and the reasons set forth above, the examiner maintains the position that, at the time of the invention, method of claims 41-42 would have been an obvious variation of the claimed method of Anderton.

Conclusion

[17] Status of the claims:

- Claims 22, 26-27, 31-36, 38-46, and 53-55 are pending.
- Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from consideration.
- Claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656